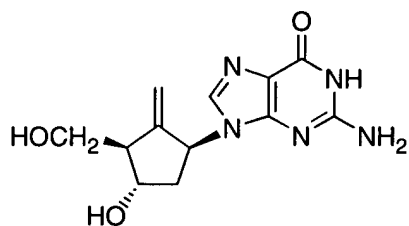


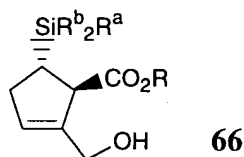
In the Claims:

1. (Currently amended) A process for the preparation of entecavir having the formula



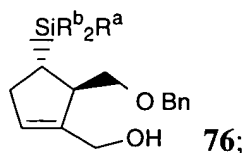
**21**, comprising:

(a) treating an ester of the formula

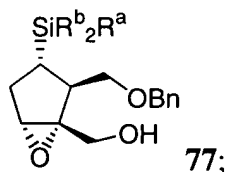


wherein  $R^a$  is allyl, phenyl,  $C_1$  to  $C_6$  alkylphenyl, or  $C_1$  to  $C_6$  alkoxyphenyl;  $R^b$  is  $C_1$  to  $C_6$  alkyl; and  $R$  is  $C_1$  to  $C_4$  alkyl or benzyl;

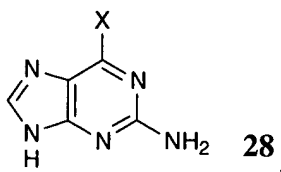
with an enol ether of acetone and an acid to protect the hydroxy group, followed by treatment with a hydride reagent to reduce the carboxylic acid ester moiety, and then alkylating the resulting alcohol with a benzyl halide and removing the enol ether hydroxy protecting group to give an allylic alcohol of the formula



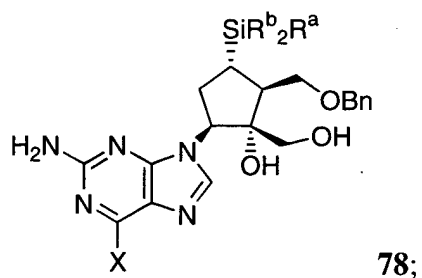
(b) epoxidizing the product from step (a) with a diastereoselective epoxidation to give a cyclopentane epoxide having the formula



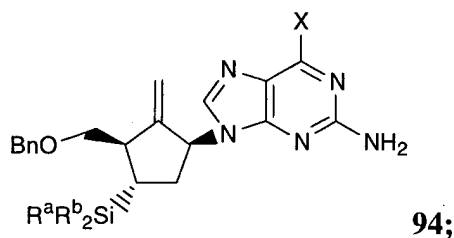
(c) treating the cyclopentane epoxide from step (b) with an alkali metal salt of a purine compound of formula



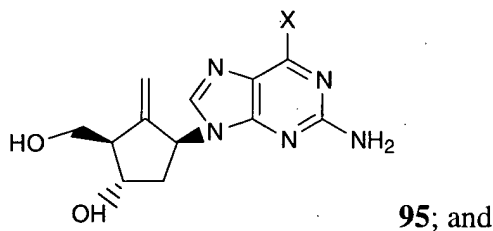
wherein X is Cl, I, or benzyloxy, to give a compound of formula



(d) when X is Cl or I, converting the vicinal diol of formula **78** to the methylene compound of formula,

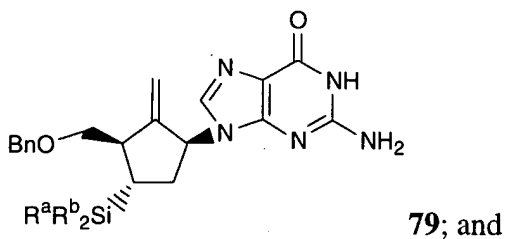


(e) hydrolyzing the benzyl ether moiety on the primary alcohol of compound **94** and converting the silane moiety of compound **95** to a hydroxy moiety to give a compound of formula,



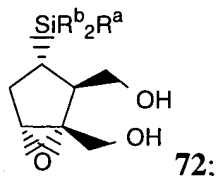
(f) hydrolyzing the chloro or iodo moiety X to provide the compound of formula **21**; or

(d') when X is benzyloxy, converting the vicinal diol of formula **78** to the methylene compound of formula

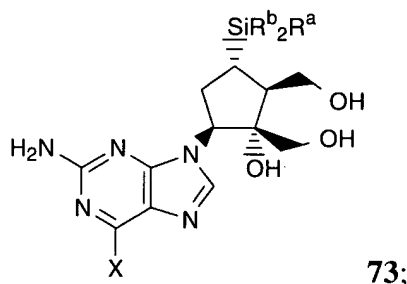


(e') hydrolyzing the benzyl ether moiety on the primary alcohol of compound **79** and converting the silane moiety to a hydroxy moiety to provide the compound of formula **21**; or

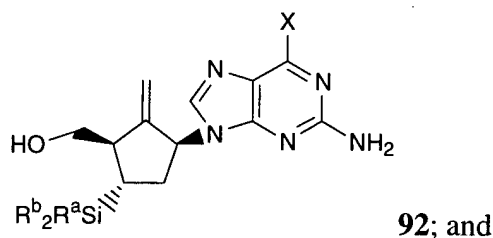
(a'') epoxidizing the ester of formula **66** with a diastereoselective epoxidation followed by reduction, to give a cyclopentane epoxide having the ~~formul~~ formula



(b'') treating the cyclopentane epoxide from step (a'') with an alkali metal salt of the purine compound of formula **28** to give a compound of formula

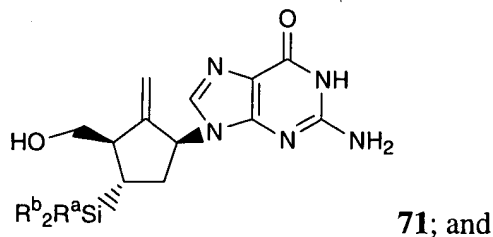


(c'') when X is Cl or I, converting the vicinal diol of formula **73** to the methylene compound of formula



(d'') converting the silane moiety of compound **92** to a hydroxy moiety and hydrolyzing the chloro or iodo moiety X to provide the compound of formula **21**; or

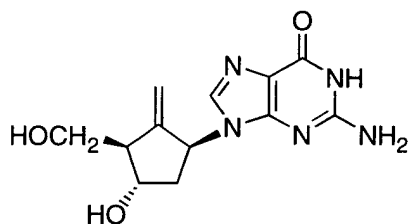
(c''') when X is benzyloxy, converting the vicinal diol of formula **73** to the methylene compound of formula



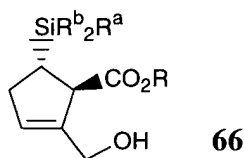
(d''') converting the silane moiety of compound **71** to a hydroxy moiety to provide the compound of formula **21**.

2. (Original) The process of Claim 1, in which, in steps (b) and (a''), the diastereoselective epoxidation is performed with a peracid or with a homochiral diester of tartaric acid, a hydroperoxide, and a metal catalyst.

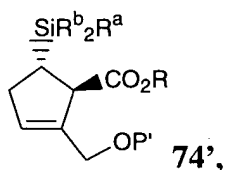
3. (Original) A process for the preparation of entecavir having the formula



(a) protecting the hydroxy moiety of an ester of the formula

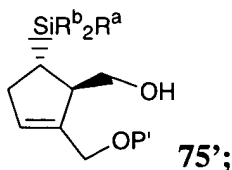


wherein  $R^a$  is allyl, phenyl,  $C_1$  to  $C_6$  alkylphenyl, or  $C_1$  to  $C_6$  alkoxyphenyl;  $R^b$  is  $C_1$  to  $C_6$  alkyl; and  $R$  is  $C_1$  to  $C_4$  alkyl or benzyl, to provide a compound of formula

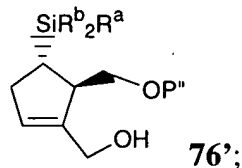


wherein  $P'$  is a protecting group;

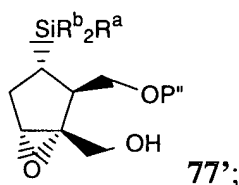
(b) reducing the carboxylic ester moiety of the compound **74'** with at least one a reducing reagent to provide a compound of formula,



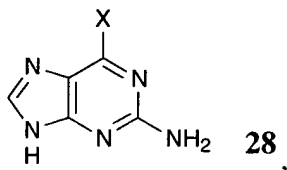
(c) protecting the unprotected hydroxy moiety of compound **75'**, with a protecting group P'' that is resistant to conditions used to remove P', then removing the protecting group P' of the compound of **75'**, to provide the compound having the formula,



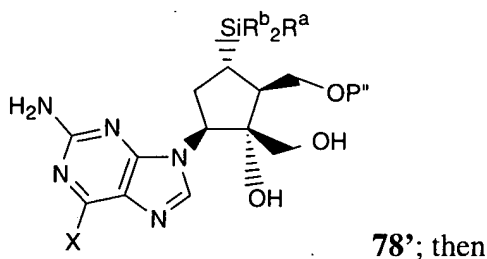
(d) epoxidizing the product from step (c) with a diastereoselective epoxidation to give a cyclopentane epoxide having the formula



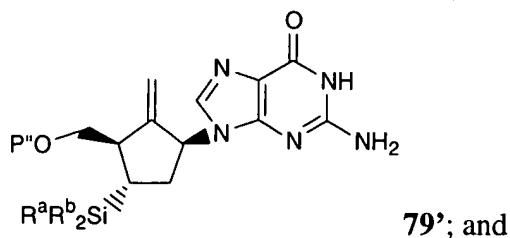
(e) treating the cyclopentane epoxide from step (d) with an alkali metal salt of a purine compound of formula



wherein X is Cl, I, or benzyloxy; to give a compound of formula

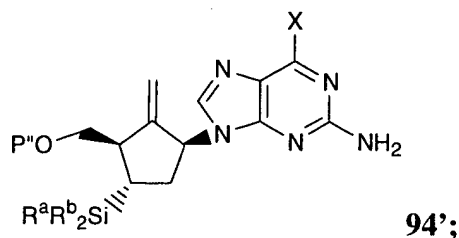


(f) when X is benzyloxy, converting the vicinal diol of formula **78'** to provide the methylene compound of formula

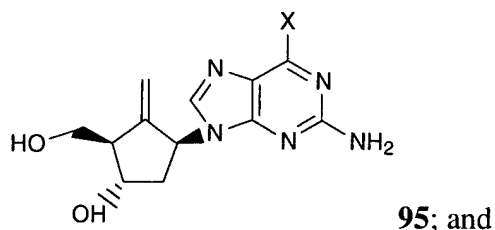


(g) removing the protecting group P'' on the primary alcohol of compound **79** and converting the silane moiety to a hydroxy moiety to provide the compound of formula **21**;  
or

(f') when X is Cl or I, converting the vicinal diol of formula **78'** to provide the methylene compound of formula,



(g') removing the protecting group P'' on the primary alcohol of compound **94'** and converting the silane moiety to a hydroxy group to give a compound of formula,



(h') hydrolyzing the chloro or iodo moiety X to provide the compound of formula **21**.

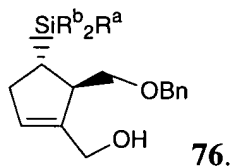
4. (Original) The process of Claim 3, wherein, in step (g), the protecting group P'' on the primary alcohol of compound **79'** is benzyl, said step of converting the silane moiety of compound **79** to a hydroxy group is achieved with protodesilylation and oxidation, and said benzyl protecting group is removed upon protodesilylation.

5. (Original) The process of Claim 3, wherein the protecting group P'' on the primary alcohol of compound **79'** is removed after the silane moiety is converted to a hydroxy moiety.

6. (Original) The process of Claim 3, wherein in step (a), the hydroxy moiety is protected as a MOP by treatment with 2-methoxypropene and a catalytic amount of a weak acid.

7. (Original) The process of Claim 3, wherein in step (b), the carboxylic ester moiety of the compound **74'** is reduced with a hydride reagent selected from at least one of sodium bis(2-methoxyethoxy)aluminum hydride and lithium aluminum hydride in the presence of a base.

8. (Original) The process of Claim 3, wherein in step (c), the unprotected hydroxy moiety is protected as a benzyl ether upon treatment with a base and a benzyl halide, wherein, removal of the protecting group P' of the compound of **75'** provides the allylic alcohol having the formula,



9. (Original) The process of Claim 8, wherein the base is selected from at least one of potassium *tert*-butoxide, sodium hydride, KHMDS, and aqueous NaOH, and the benzyl halide is benzyl bromide or benzyl chloride.

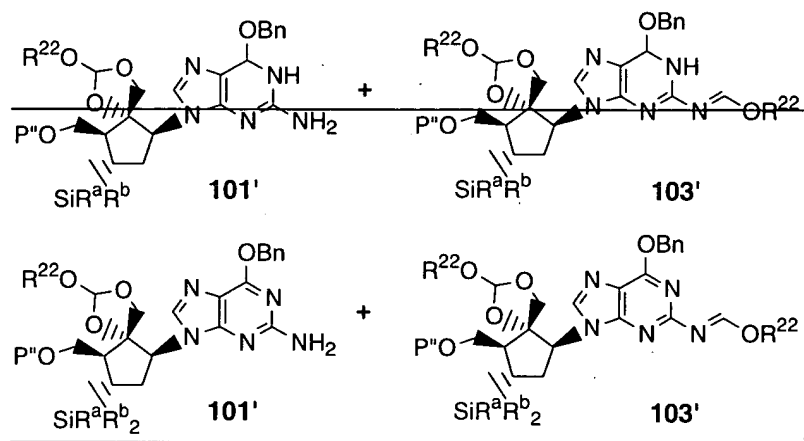
10. (Original) The process of Claim 3, in which in step (d), the diastereoselective epoxidation is performed by treatment with a peracid.

11. (Original) The process of Claim 3, in which in step (d), the diastereoselective epoxidation is performed by treatment with a homochiral diester of tartaric acid, a hydroperoxide, and a metal catalyst

12. (Original) The process of Claim 11, wherein the homochiral diester of tartaric acid is (-)-diisopropyl tartrate, the hydroperoxide is *tert*-butylhydroperoxide or  $\alpha,\alpha$ -dimethylbenzylhydroperoxide, and the metal catalyst is titanium (IV) isopropoxide.

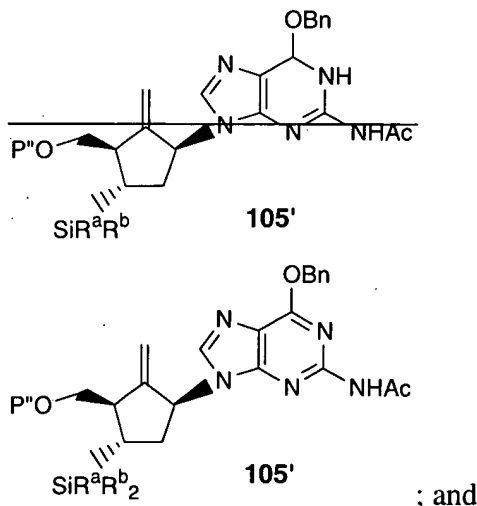
13. The process of Claim 3, wherein in step (e), the cyclopentane epoxide from step (d) is treated with 2-amino-6-benzyloxypurine in dichloromethane.

14. (Currently Amended) The process of Claim 3, wherein X is benzyloxy and in step (f), the compound **78'** is converted to the methylene compound of formula **79'** by (f)(i) treating compound **78'** with an orthoformate derivative in an inert solvent to produce a diastereomixture of dioxolanes having the formulae **101'** and **103'**,



wherein R<sup>22</sup> is C<sub>1-4</sub>alkyl or -C(=O)C<sub>1-4</sub>alkyl;

(f)(ii) treating the product from step (f)(i) with an acetic anhydride in the presence of at least one antioxidant to produce an alkene compound having the formula **105'**;



(f) (iii) treating the product from step (f)(ii) with an acid to hydrolyze the 6-benzyloxy and N-acetyl groups to provide the compound of formula **79'**.

15. The process of Claim 14, wherein in step (f)(i), the orthoformate derivative is selected from at least one of diethoxymethyl acetate, diisopropoxyethyl acetate, TMOF, TEOF, and TiPOF.

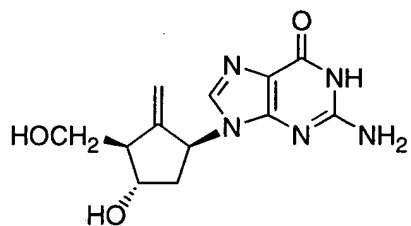
16. The process of Claim 14, wherein in step (f)(ii), at least one antioxidant is selected from BHT and benzoic acid.

17. The process of Claim 3, in which the step of converting the compound **79'** to compound **21** is achieved with protodesilylation and oxidation, wherein the protodesilylation is performed with KOH or NaOH in solvent, or with TFA, and the primary alcohol moiety is deprotected after the silane moiety is converted to a hydroxy group, to provide the compound of formula **21**.

18. The process of Claim 3, in which the step of converting the compound **79'** to compound **21** is achieved with protodesilylation and oxidation, wherein the step of protodesilylation is achieved with at least one acid selected from boron trifluoride-acetic acid complex and a Bronsted acid.

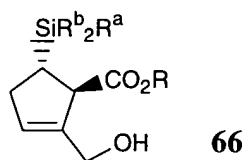
19. The process of Claim 3, in which the step of converting the compound **79'** to compound **21** is achieved with protodesilylation and oxidation, and the oxidation is achieved with hydrogen peroxide in the presence of potassium bicarbonate and optionally potassium fluoride.

20. (Currently Amended) A process for the preparation of entecavir having the formula

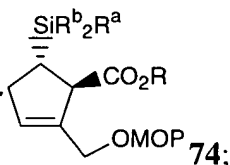


**21**, comprising:

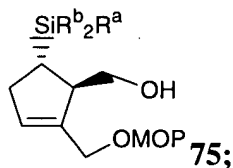
(a) treating an ester of the formula



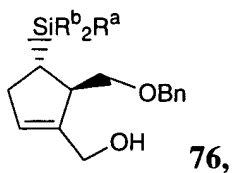
wherein  $R^a$  is allyl, phenyl,  $C_1$  to  $C_6$  alkylphenyl, or  $C_1$  to  $C_6$  alkoxyphenyl;  $R^b$  is  $C_1$  to  $C_6$  alkyl; and  $R$  is  $C_1$  to  $C_4$  alkyl or benzyl; with 2-methoxypropene and a catalytic amount of a weak acid to provide a compound of formula



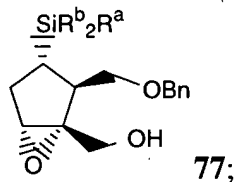
(b) reducing the carboxylic ester moiety of the compound **74** with a hydride reagent selected from at least one of sodium bis(2-methoxyethoxy)aluminum hydride and lithium aluminum hydride, in the presence of a base to provide a compound of formula,



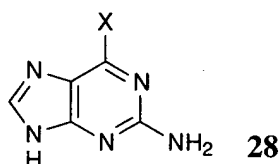
(c) protecting the unprotected hydroxy moiety of compound **75**, as a benzyl ether upon treatment of compound **75** with a base and a benzyl halide, then removing the MOP group of the compound **75**, to provide the allylic alcohol having the formula,



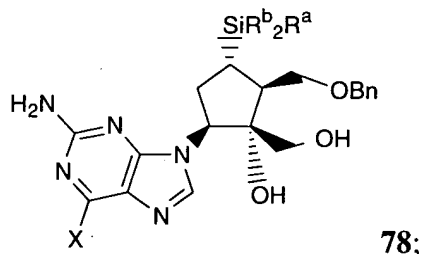
(d) epoxidizing the product from step (c) with (-)-diisopropyl tartrate, *tert*-butylhydroperoxide or cumene hydroperoxide, and titanium (IV) isopropoxide, to give a cyclopentane epoxide having the formula



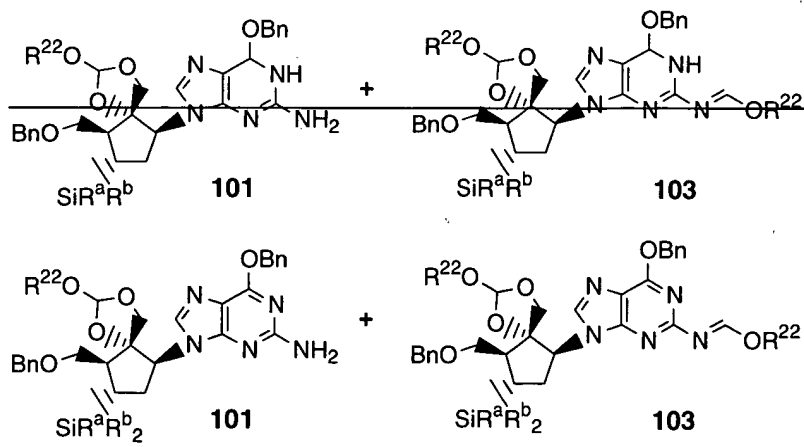
(e) treating the cyclopentane epoxide from step (d) with an alkali metal salt of a purine compound of formula



wherein X is benzyloxy; to give a compound of formula

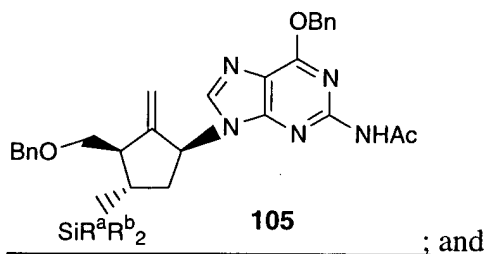
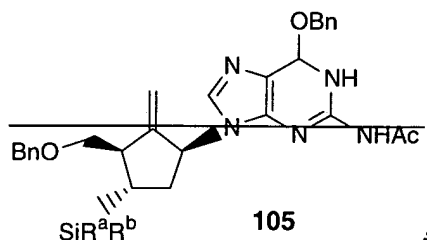


(f)(i) treating compound **78** with an orthoformate derivative selected from diethoxymethyl acetate and diisopropoxyxymethyl acetate in an inert solvent to produce a diastereomixture of dioxolanes having the formulae **101** and **103**,

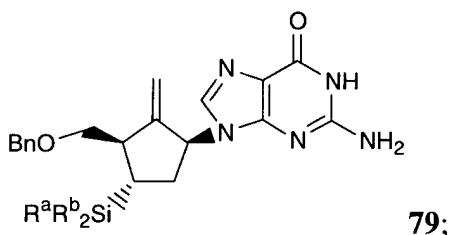


wherein  $R^{22}$  is ethyl,  $-C(=O)ethyl$ , isopropyl, or  $-C(=O)isopropyl$ ;

(f)(ii) treating the product from step (f)(i) with an acetic anhydride in the presence of BHT to produce an alkene compound having the formula **105**;

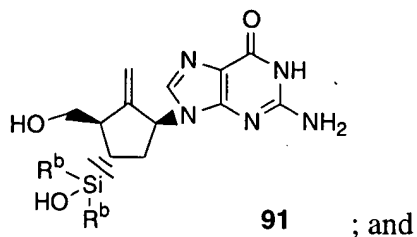


(f) (iii) treating the product from step (f)(ii) with an acid to hydrolyze the 6-benzyloxy and N-acetyl groups and provide the compound of formula **79**,



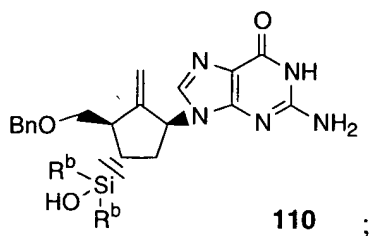
(g) converting the silane moiety to a hydroxy moiety by protodesilylating the silane moiety of compound **79** upon treatment with at least one reagent effective to achieve protodesilylation, followed by oxidation with a peroxide, and debenzylating compound **79**, wherein debenzylation may be achieved upon protodesilylation, to provide the compound of formula **21**.

21. The process of Claim 20, in which step (g) comprises treating compound **79** with an acid selected from boron trifluoride-acetic acid complex and a Bronsted acid, wherein said step of protodesilylation removes the benzyl protecting group of compound **79** to provide the compound of formula **91**,

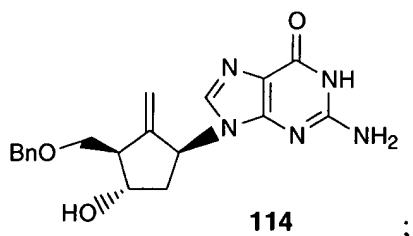


oxidizing the compound **91** with hydrogen peroxide in the presence of potassium bicarbonate and potassium fluoride to provide the compound **21**.

22. The process of Claim 20, in which step (g) comprises treating compound **79** with potassium hydroxide or sodium hydroxide in solvent, or TFA to provide the compound of formula **110**,



oxidizing compound **110** with hydrogen peroxide in the presence of potassium bicarbonate and potassium fluoride to provide the compound **114**;



and debenzylating compound **114** to provide compound **21**.

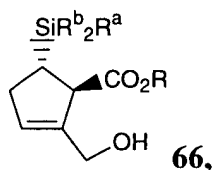
23. A method for isolating entecavir or an entecavir intermediate from a diluted mixture, the diluted mixture comprising entecavir and water or a mixture comprising an entecavir intermediate and other process reagents comprising:

- (a) adsorbing the diluted mixture onto a hydrophobic resin bed;
- (b) washing the resin bed with water to remove salt; and

(c) eluting the entecavir or entecavir intermediate from the resin bed with an organic solvent.

24. The method of Claim 23 wherein the hydrophobic resin is a brominated styrene based resin.

25. A process for the preparation of an ester of the formula



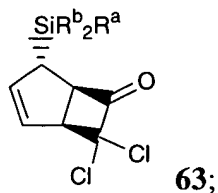
wherein  $R^a$  is alkyl, phenyl,  $C_1$  to  $C_6$  alkylphenyl, or  $C_1$  to  $C_6$  alkoxyphenyl;  $R^b$  is  $C_1$  to  $C_6$  alkyl; and  $R$  is  $C_1$  to  $C_4$  alkyl or benzyl comprising:

(a) reacting a cyclopentadienide ion



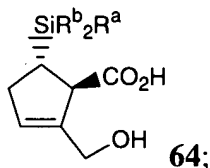
with a silylating reagent having the formula  $R^a(R^b)_2Si-Y$ , wherein  $Y$  is a leaving group; and

(b) reacting the product of step (a) with a ketene to give a cyclobutanone of the formula

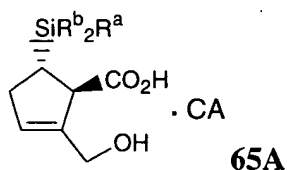


(c) treating the product from step (b) with a base effective for opening the cyclobutanone ring;

(d) reducing the product from step (c) with a reducing agent to give a racemic carboxylic acid of the formula



(e) resolving the product from step (d) by treatment with a chiral amine and separation of the resulting diastereomeric salts to give a compound of formula



wherein CA represents a chiral amine; and

(f) heating the product from step (e) in a solution of an acidic solution to give the ester product of formula **66**.

26. The process of Claim 25, in which, in step (b), the ketene is formed from dichloroacetyl chloride and a base.

27. The process of Claim 25, in which, in step (c), the base is potassium carbonate in *t*-butanol.

28. The process of Claim 25, in which, in step (d), the reducing reagent is  $\text{NaBH}_4$ .

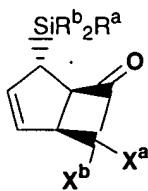
29. The process of Claim 25, in which, in step (e), the chiral amine is selected from the group consisting of R,R-(-)-2-amino-1-(4-nitrophenyl)-1,3-propanediol, (1R,2R)-(+)-1,2-diphenylethylenediamine, (R)-(-)-1-cyclohexylethylamine, D-threo-2-amino-1-(4-nitrophenyl)-1,3-propanediol, (1S,2S)-(+)-1,2-diaminocyclohexane, dehydroabietylamine, (1R,2R)-1,2-diaminomethylcyclohexane, cichonidine, and cinchonine.

30. The process of Claim 25, in which, in step (f), the acidic solution comprises a solution of an alcohol, R-OH, wherein R is  $\text{C}_1$  to  $\text{C}_4$  alkyl or benzyl, and an acid.

31. The process of Claim 25, in which,  
in step (b), the ketene is formed from dichloroacetyl chloride and a base;  
in step (c), the base is potassium carbonate in *t*-butanol;

in step (d), the reducing reagent is  $\text{NaBH}_4$ ;  
 in step (e), the chiral amine is R,R-(-)-2-amino-1-(4-nitrophenyl)-1,3-propanediol;  
 and  
 in step (f), the acidic solution comprises a solution of an alcohol,  $\text{R-OH}$ , wherein  
 R is  $\text{C}_1$  to  $\text{C}_4$  alkyl or benzyl, and an acid.

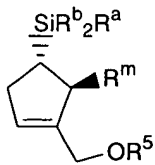
32. A compound of formula



wherein:

$\text{R}^a$  is allyl, phenyl,  $\text{C}_1$  to  $\text{C}_6$  alkylphenyl or  $\text{C}_1$  to  $\text{C}_6$  alkoxyphenyl;  
 $\text{R}^b$  is  $\text{C}_1$  to  $\text{C}_6$  alkyl; and  
 $\text{X}^a$  and  $\text{X}^b$  are halide.

33. A compound of formula



or a salt thereof wherein:

$\text{R}^a$  is allyl, phenyl,  $\text{C}_1$  to  $\text{C}_6$  alkylphenyl or  $\text{C}_1$  to  $\text{C}_6$  alkoxyphenyl;  
 $\text{R}^b$  is  $\text{C}_1$  to  $\text{C}_6$  alkyl;  
 $\text{R}^m$  is  $-\text{CO}_2\text{R}^6$  or  $-\text{CH}_2\text{OR}^6$ ;  
 $\text{R}^5$  is hydrogen or a hydroxy protecting group; and  
 $\text{R}^6$  is hydrogen,  $\text{C}_1$  to  $\text{C}_4$  alkyl, or benzyl.

34. A compound of Claim 33 wherein:

$\text{R}^m$  is  $-\text{CO}_2\text{R}^6$ ; and  
 $\text{R}^5$  and  $\text{R}^6$  are both hydrogen.

35. The compound of Claim 34 wherein:

$\text{R}^a$  is phenyl; and

$R^b$  is methyl.

36. A compound of Claim 33 as a salt with a chiral amine selected from the group consisting of R,R-(-)-2-amino-1-(4-nitrophenyl)-1,3-propanediol, (1R,2R)-(+)-1,2-diphenylethylenediamine, (R)-(-)-1-cyclohexylethylamine; D-threo-2-amino-1-(4-nitrophenyl)-1,3-propanediol, (1S,2S)-(+)-1, 2-diaminocyclohexane, dehydroabietylamine, (1R,2R)-1, 2-diaminomethylcyclohexane, cinchonidine, and cinchonine.

37. The compound of Claim 36 wherein:

$R^m$  is  $-\text{CO}_2R^6$ ;

$R^5$  and  $R^6$  are both hydrogen;

$R^a$  is phenyl;

$R^b$  is methyl; and

the chiral amine is R,R-(-)-2-amino-1-(4-nitrophenyl)-1,3-propanediol.

38. The compound of Claim 33 wherein:

$R^m$  is  $-\text{CH}_2\text{OR}^6$ ;

$R^5$  is hydrogen; and

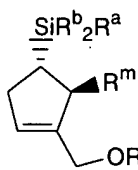
$R^6$  is benzyl.

39. The compound of Claim 38 wherein:

$R^a$  is phenyl; and

$R^b$  is methyl.

40. A compound having the formula



or a salt thereof wherein:

$R^a$  is phenyl;

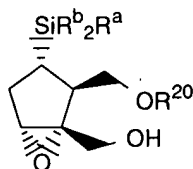
$R^b$  is  $C_1$  to  $C_6$  alkyl;

$R^m$  is  $-\text{CO}_2R^6$  or  $-\text{CH}_2\text{OR}^6$ ;

$R^5$  is hydrogen or a hydroxy protecting group; and

$R^6$  is hydrogen,  $\text{C}_1$  to  $\text{C}_4$  alkyl, or benzyl, said compound produced according to the process of claim 22.

41. A compound of formula



wherein:

$R^a$  is alkyl, phenyl,  $\text{C}_1$  to  $\text{C}_6$  alkylphenyl, or  $\text{C}_1$  to  $\text{C}_6$  alkoxyphenyl;

$R^b$  is  $\text{C}_1$  to  $\text{C}_6$  alkyl; and

$R^{20}$  is hydrogen or benzyl.

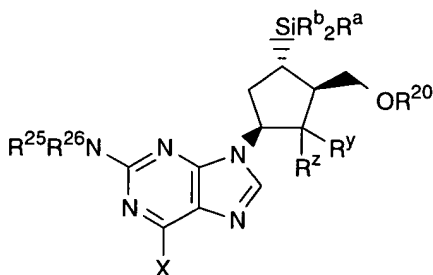
42. The compound of Claim 41 wherein:

$R^a$  is phenyl;

$R^b$  is methyl; and

$R^{20}$  is benzyl.

43. A compound of formula



or a salt thereof wherein:

$R^a$  is alkyl, phenyl,  $\text{C}_1$  to  $\text{C}_6$  alkylphenyl, or  $\text{C}_1$  to  $\text{C}_6$  alkoxyphenyl;

$R^b$  is  $\text{C}_1$  to  $\text{C}_6$  alkyl;

$R^{20}$  is hydrogen or benzyl;

$X$  is  $\text{Cl}$ ,  $\text{I}$ , or benzyloxy;

$R^y$  and  $R^z$  are taken together to form methylene ( $=\text{CH}_2$ ), or  $R^y$  is  $\text{OR}^{23}$ , and

$R^z$  is  $-\text{CH}_2\text{OR}^{24}$ , wherein  $R^{23}$  and  $R^{24}$  are each hydrogen or are taken together to

form a ring to define a dioxolane, said dioxolane being optionally substituted with  $-O(C_{1-4}alkyl)$  or  $-O(C=O)(C_{1-4}alkyl)$ ; and

$R^{25}$  and  $R^{26}$  are both hydrogen, or one of  $R^{25}$  and  $R^{26}$  is hydrogen and the other is acyl; or  $R^{25}$  and  $R^{26}$  are taken together to form  $=CH(OC_{1-4}alkyl)$  or  $=CH(OC(=O)C_{1-4}alkyl)$ .

44. The compound of Claim 43 wherein:

$R^a$  is phenyl;

$R^b$  is methyl; and

X is benzyloxy.

45. The compound of claim 44 in which

$R^{20}$  is benzyl;

$R^y$  is OH, and  $R^z$  is  $-CH_2OH$ , and

$R^{25}$  and  $R^{26}$  are both hydrogen.

46. The compound of Claim 43 wherein:

$R^a$  is phenyl;

$R^b$  is methyl;

X is benzyloxy;

$R^y$  is  $OR^{23}$ , and  $R^z$  is  $-CH_2OR^{24}$ , wherein  $R^{23}$  and  $R^{24}$  combine to form a dioxolane optionally substituted with  $-O(C_{1-4}alkyl)$  or  $O(C=O)(C_{1-4}alkyl)$ ; and

$R^{25}$  and  $R^{26}$  are both hydrogen, or  $R^{25}$  and  $R^{26}$  are taken together to form  $=CH(OC_{1-4}alkyl)$  or  $=CH(O(C=O)C_{1-4}alkyl)$ .

47. The compound of Claim 43 wherein:

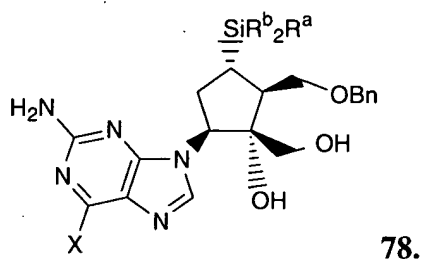
$R^a$  is phenyl;

$R^b$  is methyl;

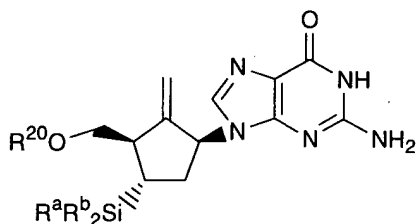
X is benzyloxy;

$R^y$  and  $R^z$  are taken together to form methylene; and  
 $R^{25}$  is hydrogen and  $R^{26}$  is acyl.

48. The compound of Claim 43 having the formula,



49. A compound of formula



or a salt thereof, wherein:

$R^a$  is alkyl, phenyl,  $C_1$  to  $C_6$  alkylphenyl, or  $C_1$  to  $C_6$  alkoxyphenyl;

$R^b$  is  $C_1$  to  $C_6$  alkyl; and

$R^{20}$  is hydrogen or benzyl.

50. The compound of Claim 49 wherein:

$R^a$  is phenyl;

$R^b$  is methyl; and

$R^{20}$  is hydrogen.

51. The compound of Claim 49 wherein:

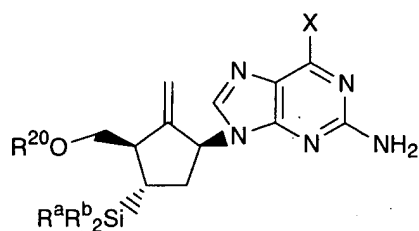
$R^a$  is phenyl;

$R^b$  is methyl; and

$R^{20}$  is benzyl.

52. The methanesulfonate salt of the compound of Claim 51.

53. A compound of formula



or a salt thereof, wherein:

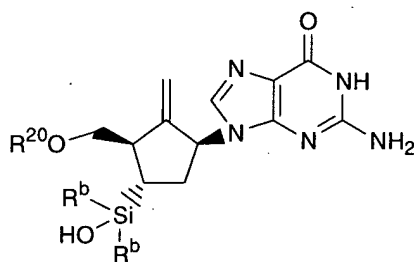
X is Cl or I;

R<sup>a</sup> is alkyl, phenyl, C<sub>1</sub> to C<sub>6</sub> alkylphenyl, or C<sub>1</sub> to C<sub>6</sub> alkoxyphenyl;

R<sup>b</sup> is C<sub>1</sub> to C<sub>6</sub> alkyl; and

R<sup>20</sup> is hydrogen or benzyl.

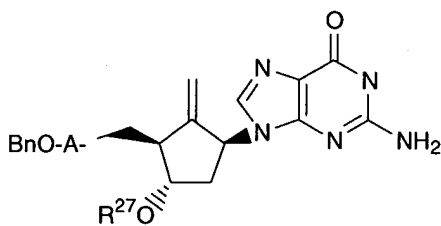
54. A compound of formula



wherein R<sup>b</sup> is C<sub>1</sub> to C<sub>6</sub> alkyl; and R<sup>20</sup> is hydrogen or benzyl, or a salt thereof.

55. The compound of Claim 54 wherein R<sup>b</sup> is methyl.

56. A compound of formula



or a salt thereof, wherein:

A is CH<sub>2</sub> or a bond;

R<sup>27</sup> is hydrogen, benzyl, or SiR<sup>d</sup><sub>2</sub>R<sup>c</sup>;

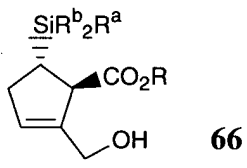
R<sup>c</sup> is C<sub>1</sub> to C<sub>4</sub> alkyl or phenyl; and

R<sup>d</sup> is C<sub>1</sub> to C<sub>3</sub> alkyl.

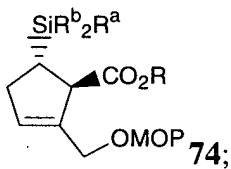
57. A compound of claim 56, in which A is a bond, and R<sup>27</sup> is hydrogen.

58. A method for making a compound of formula **78**, according to Claim 48, comprising,

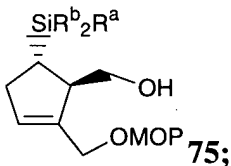
(a) treating an ester of the formula



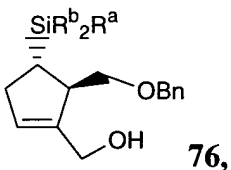
wherein R<sup>a</sup> is allyl, phenyl, C<sub>1</sub> to C<sub>6</sub> alkylphenyl, or C<sub>1</sub> to C<sub>6</sub> alkoxyphenyl; R<sup>b</sup> is C<sub>1</sub> to C<sub>6</sub> alkyl; and R is C<sub>1</sub> to C<sub>4</sub> alkyl or benzyl; with 2-methoxypropene and a catalytic amount of a weak acid to provide a compound of formula



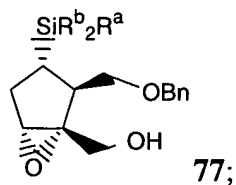
(b) reducing the carboxylic ester moiety of the compound **74** with at least one hydride reagent to provide a compound of formula,



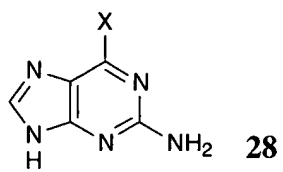
(c) protecting the unprotected hydroxy moiety of compound **75**, as a benzyl ether upon treatment of compound **75** with a base and a benzyl halide, then removing the MOP group of the compound **75**, to provide the allylic alcohol having the formula,



(d) epoxidizing the product from step (c) with a diastereoselective epoxidation, to give a cyclopentane epoxide having the formula

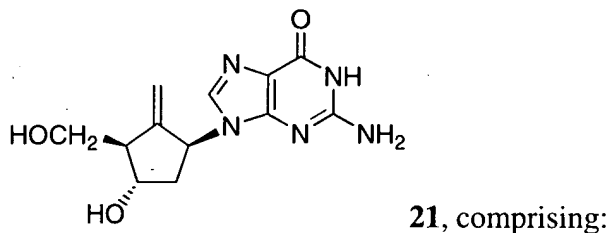


(e) treating the cyclopentane epoxide from step (d) with an alkali metal salt of a purine compound of formula

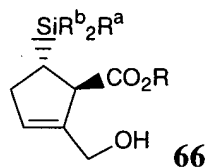


wherein X is benzyloxy; I, or Cl, to give a compound of formula **78**.

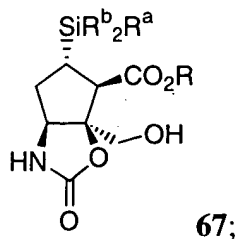
59. A process for the preparation of entecavir having the formula



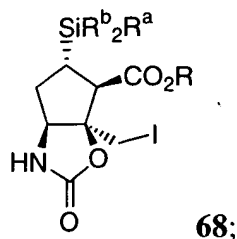
(a) converting an ester having the formula



wherein R is C<sub>1</sub> to C<sub>4</sub> alkyl, or benzyl; R<sup>a</sup> is allyl, phenyl, C<sub>1</sub> to C<sub>6</sub> alkylphenyl or C<sub>1</sub> to C<sub>6</sub> alkoxyphenyl, and R<sup>b</sup> is C<sub>1</sub> to C<sub>6</sub> alkyl, under aminohydroxylation conditions to give an oxazolidinone having the formula

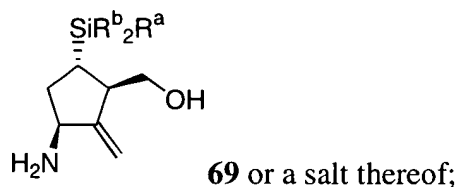


(b) converting the alcohol of the oxazolidinone of formula **67** with an iodide salt to give an iodide having the formula

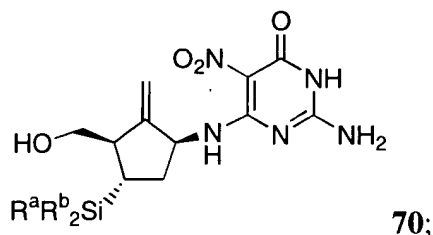


(c) treating the iodide of formula **68** with zinc and acetic acid;

(d) treating the product of step (c) with a hydride reagent to reduce the ester moiety to an alcohol and give a methylene compound of formula

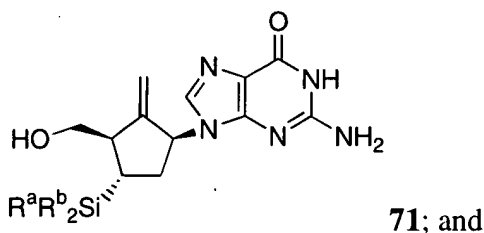


(e) reacting the methylene compound of formula **69** with 6-chloro-2-amino-5-nitro-4(3H)-pyrimidinone in the presence of base to give a pyrimidine compound having the formula



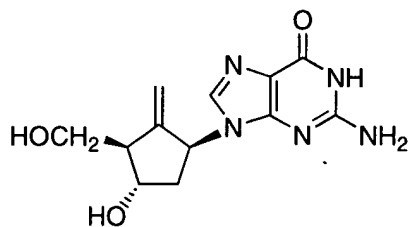
(f) treating the pyrimidine compound of formula **70** with a reducing agent to reduce the nitro moiety to an amine;

(g) cyclizing the product of step (f) with an orthoformate derivative and an acid to give a methylene compound having the formula



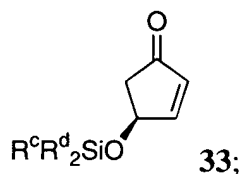
(h) converting the silane moiety of the compound of formula **71** to a hydroxy moiety and providing the compound of formula **21**.

60. A process for the preparation of entecavir having the formula

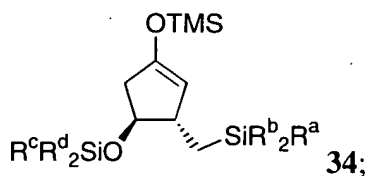


**21**, comprising:

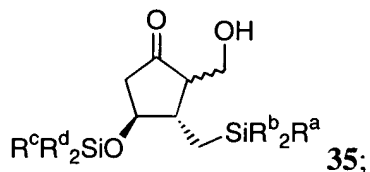
(a) treating 4-(S)-hydroxy-2-cyclopenten-1-one with a silylating reagent of the formula  $R^cR^d_2SiY$  and a trialkylamine base wherein  $R^c$  is  $C_1$  to  $C_4$  alkyl or phenyl,  $R^d$  is  $C_1$  to  $C_3$  alkyl, and  $Y$  is a leaving group to give the compound of formula



(b) treating the product from step (a) with a Grignard reagent prepared from a (halomethyl)silane reagent of the formula  $R^aR^b_2SiCH_2X'$ , wherein  $R^a$  is allyl, phenyl,  $C_1$  to  $C_6$  alkylphenyl or  $C_1$  to  $C_6$  alkoxyphenyl;  $R^b$  is  $C_1$  to  $C_6$  alkyl; and  $X'$  is chloro, bromo, or iodo followed by treatment with trimethylsilylating reagent to give a compound of formula

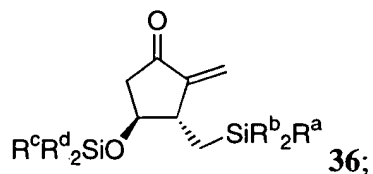


(c) formylating the compound of formula **34** to give a compound of formula

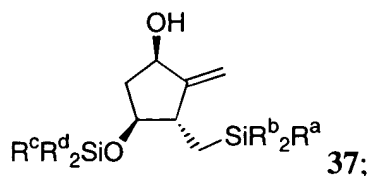


(d) treating the compound of formula **35** with a sulfonylating reagent having the formula  $R^3SO_2Cl$ , wherein  $R^3$  is  $C_1$  to  $C_4$  alkyl, trifluoromethyl, phenyl or phenyl substituted by  $C_1$  to  $C_6$  alkyl or  $C_1$  to  $C_6$  alkoxy;

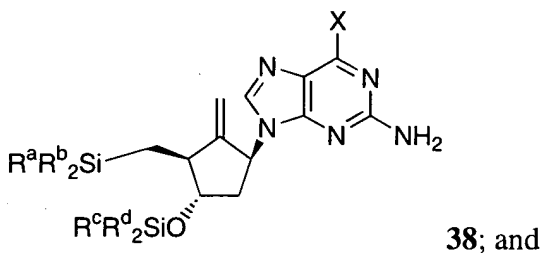
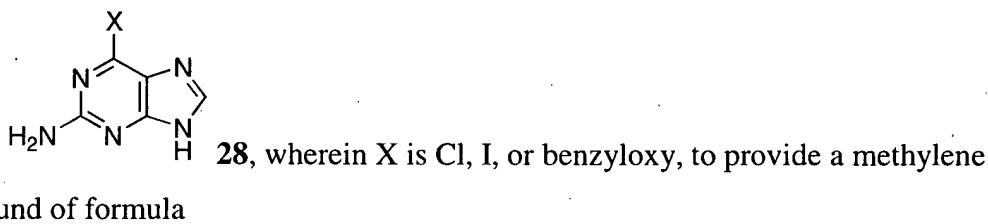
(e) reacting the product of step (d) with a strong base to eliminate a sulfonate group to provide a methylene compound of formula



(f) selectively reducing the methylene compound of formula **36** with a hydride reagent to provide an allylic alcohol of the formula

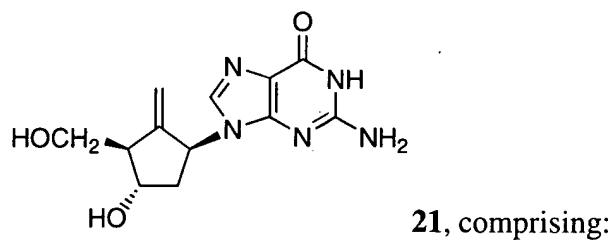


(g) condensing the allylic alcohol of the formula **37** under Mitsunobu conditions with a purine compound of formula

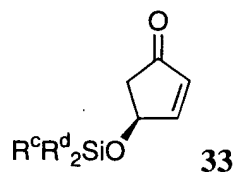


(h) converting the compound of formula **38** to the compound of formula **21**.

61. A process for the preparation of entecavir having the formula

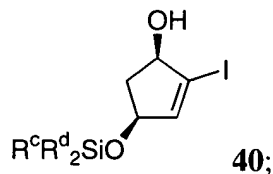


(a) reacting a cyclopentenone of the formula

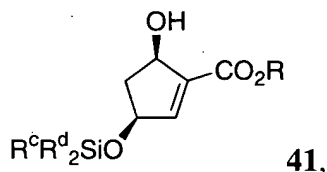


with iodine, wherein  $R^c$  is  $C_1$  to  $C_4$  alkyl, or phenyl, and  $R^d$  is  $C_1$  to  $C_3$  alkyl;

(b) reducing the carbonyl group of the product of step (a) to provide an iodo compound of formula

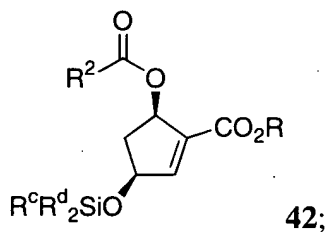


(c) converting the iodo compound of formula 40 to give a compound of formula

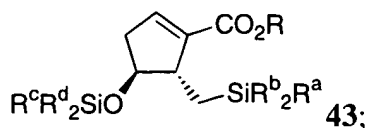


wherein  $R$  is  $C_1$  to  $C_4$  alkyl, or benzyl;

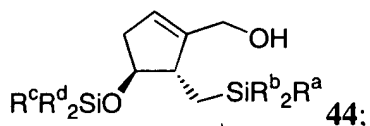
(d) acylating the compound of formula **41** with an activated acyl agent of the formula  $R^2C(O)-Y$  wherein  $R^2$  is  $C_1$  to  $C_6$  alkyl, arylalkyl or aryl, and  $Y$  is a leaving group to give a compound of formula



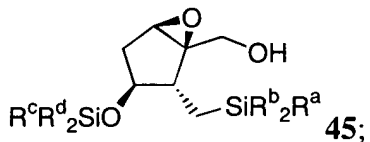
(e) treating the product of step (d) with a Grignard reagent prepared from a (halomethyl)silane reagent of the formula  $R^aR^b_2SiCH_2X'$ , wherein  $R^a$  is allyl, phenyl,  $C_1$  to  $C_6$  alkylphenyl or  $C_1$  to  $C_6$  alkoxyphenyl;  $R^b$  is  $C_1$  to  $C_6$  alkyl; and  $X'$  is chloro, bromo, or iodo to give an ester of the formula



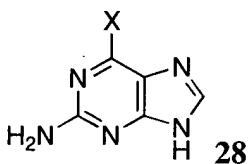
(f) reducing the ester of formula **43** with a hydride reagent to provide an allylic alcohol of the formula



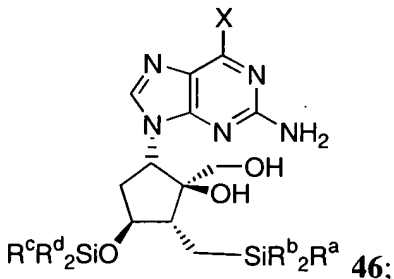
(g) epoxidizing the allylic alcohol of formula **44** with an oxidizing agent to provide a cyclopentane epoxide of the formula



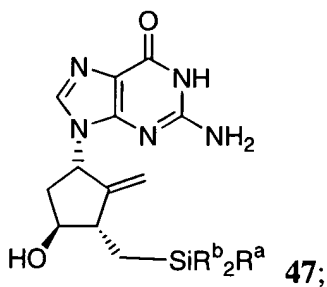
(h) reacting the cyclopentane epoxide of formula **45** with an alkali metal salt of a purine compound of formula



wherein X is Cl, I or benzyloxy, to give a compound of formula



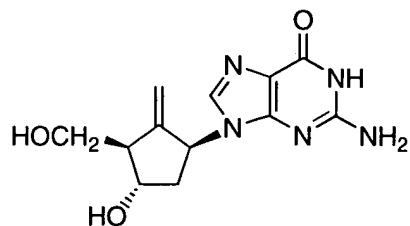
(i) converting the compound of formula **46** to a methylene compound of formula



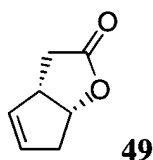
(j) treating the compound of formula **47** with an acid or base effective for protodesilylation of the silyl moiety; and

(k) oxidizing the product of step (j) to provide the compound of formula **21**.

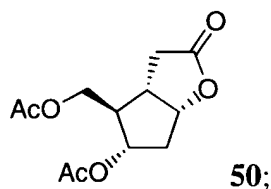
62. A process for the preparation of entecavir having the formula



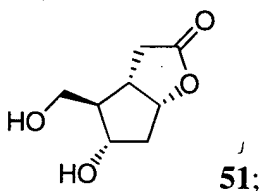
(a) treating a homochiral bicyclic lactone of the formula



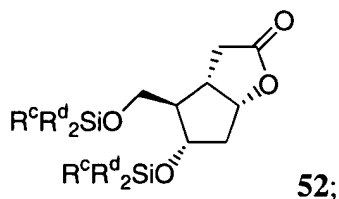
with paraformaldehyde, acetic acid, and sulfuric acid to provide a diacetate of the formula



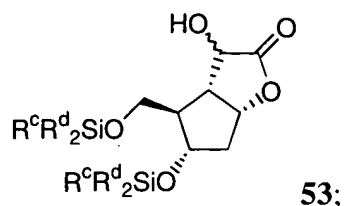
(b) treating the diacetate product of step (a) using a base in an alcohol solvent to remove the acetate protecting groups to give the compound having the formula



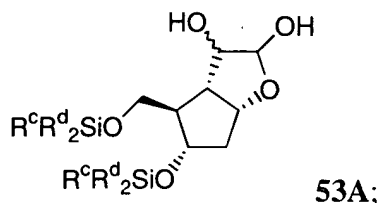
(c) treating the product of step (b) with a silylating reagent of the formula  $R^cR^d_2SiY$ , wherein  $R^c$  is linear or branched  $C_1$  to  $C_4$  alkyl, or phenyl, and  $R^d$  is linear or branched  $C_1$  to  $C_3$  alkyl and  $Y$  is a leaving group, to provide a compound of formula



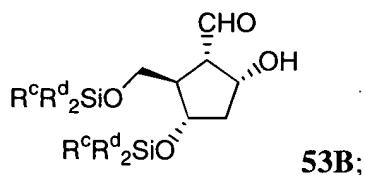
(d) treating the product of step (c) with a strong non-nucleophilic base and (1S)-(+)-(10-camphorsulfonyl)oxaziridine to give a compound of formula



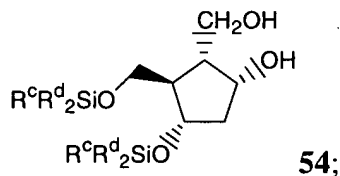
(e) reducing the lactone moiety of the product from step (d) with a hydride reagent to give a compound having the formula



(f) cleaving the product from step (e) with an oxidizing agent to give a compound of formula

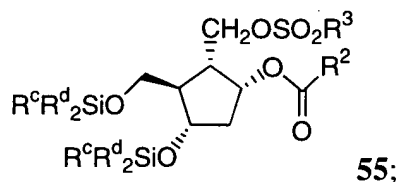


(g) reducing the product from step (f) with a hydride reagent to give a diol of the formula



(h) selectively sulfonylating the primary alcohol of the product from step (g) with a reagent of the formula  $R^3SO_2Cl$ , wherein  $R^3$  is  $C_1$  to  $C_4$  alkyl, trifluoromethyl, phenyl, or phenyl substituted by  $C_1$  to  $C_6$  alkyl or  $C_1$  to  $C_6$  alkoxy;

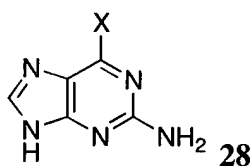
(i) acylating the secondary alcohol of the product of step (h) with an acylating agent of the formula  $R^2C(O)-Y$ , wherein  $R^2$  is  $C_1$  to  $C_6$  alkyl, arylalkyl or aryl, and Y is a leaving group to give a compound having the formula



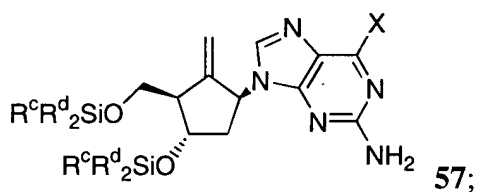
(j) treating the product from step (i) with a strong base to effect elimination and hydrolysis of the carboxylic acid ester to give the compound of formula



(k) condensing the product from step (j) with a purine compound of formula



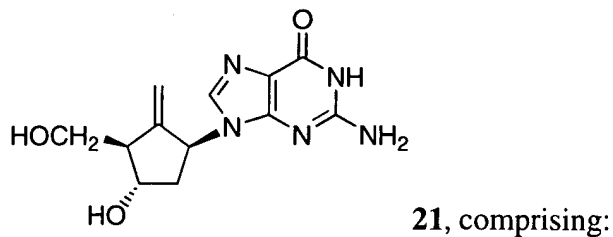
wherein X is Cl, I or benzyloxy, under Mitsunobu conditions to give a methylene compound of formula



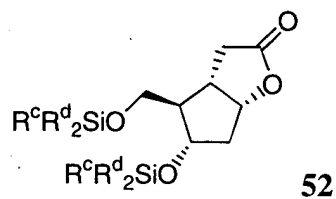
(l) removing the silyl ether protecting groups of the methylene compound of formula **57**; and

(m) hydrolyzing the 6-X group to give the compound of formula **21**.

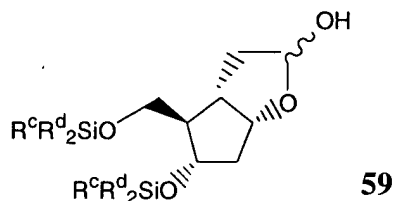
63. A process for the preparation of entecavir having the formula



(a) reducing the compound of formula

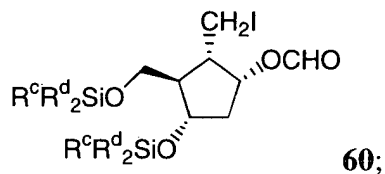


to give a lactol of the formula

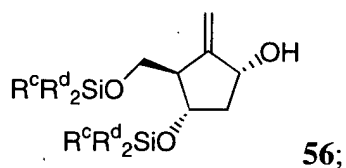


wherein  $R^c$  is a linear or branched  $C_1$  to  $C_4$  alkyl, or phenyl, and  $R^d$  is a linear or branched  $C_1$  to  $C_3$  alkyl;

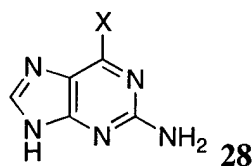
(b) iodinating the lactol product of step (a) by free radical oxidation to give an iodide compound having the formula



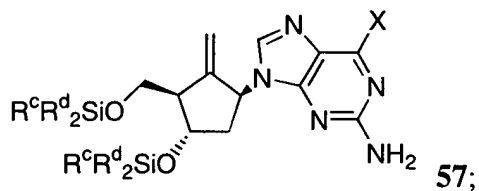
(c) treating the product from step (b) with a strong base to give the methylene compound of formula



(d) condensing the product from step (c) with a purine compound of formula



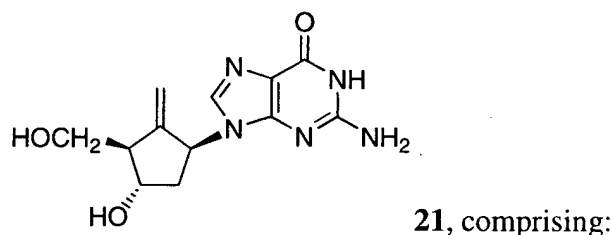
wherein X is Cl, I or benzyloxy, under Mitsunobu conditions to give a methylene compound of formula



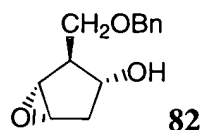
(e) removing the silyl ether protecting groups of the methylene compound of formula **57**; and

(f) hydrolyzing the 6-X group to give the compound of formula **21**.

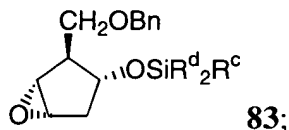
64. A process for the preparation of entecavir having the formula



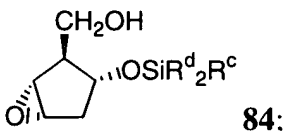
(a) silylating a compound of formula



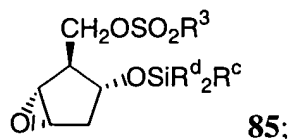
with a compound of formula  $R^cR^d_2SiY$ , wherein  $R^c$  is linear or branched  $C_1$  to  $C_4$  alkyl, or phenyl,  $R^d$  is linear or branched  $C_1$  to  $C_3$  alkyl, and Y is a leaving group, to provide a compound of formula



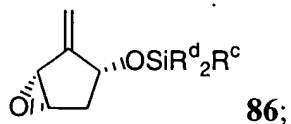
(b) reducing the product from step (a) under conditions sufficient to remove the benzyl protecting group to give a compound of formula



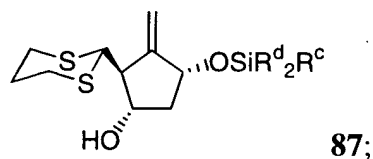
(c) converting the alcohol moiety of the product from step (b) to a sulfonate ester of the formula  $SO_2R^3$ , wherein  $R^3$  is  $C_1$  to  $C_4$  alkyl, trifluoromethyl, or phenyl substituted by  $C_1$  to  $C_6$  alkyl or  $C_1$  to  $C_6$  alkoxy to give a compound of formula



(d) treating the product from step (c) with a strong base to effect elimination of the  $R^3SO_3H$  to provide the methylene compound of formula

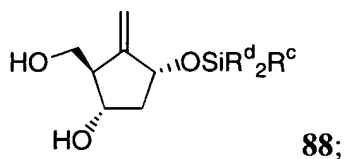


(e) treating the product from step (d) with a lithium salt of 1,3-dithiane to provide the compound of formula

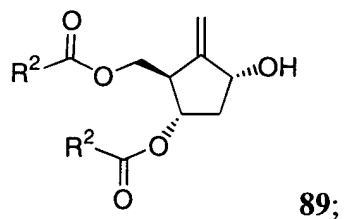


(f) hydrolyzing the dithioacetal moiety of the compound of formula **87**; and

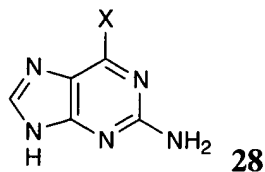
(g) treating the product of step (f) with a hydride reagent to provide a compound of formula



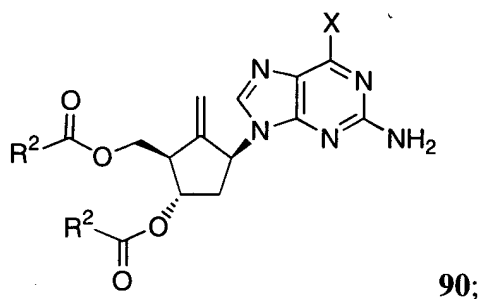
(h) acylating the compound of formula **88** with a compound having the formula  $R^2C(O)-Y$ , wherein Y is a leaving group and  $R^2$  is  $C_1$  to  $C_6$  alkyl or aryl, to give the compound of formula



(i) condensing the product from step (h) with a purine compound of formula

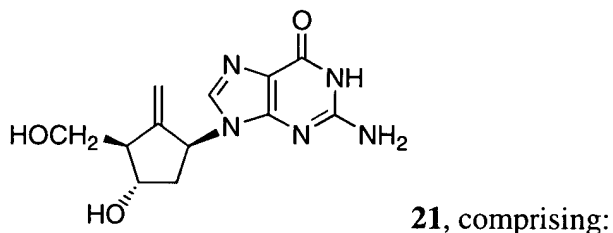


wherein X is Cl, I, or benzyloxy under Mitsunobu conditions to give a methylene compound of formula

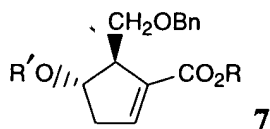


- (j) removing the acyl ester protecting groups from the methylene compound of formula **90**; and
- (k) hydrolyzing the X group to give the compound of formula **21**.

65. A process of preparing entecavir having the formula

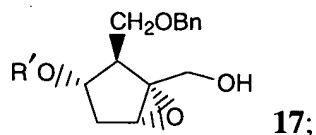


- (a) reducing an ester of the formula

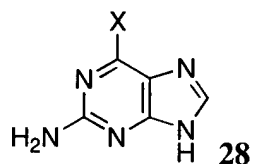


wherein R is C<sub>1</sub> to C<sub>4</sub> alkyl, or benzyl, and R' is benzyl, benzyl substituted on the phenyl moiety by C<sub>1</sub> to C<sub>6</sub> alkyl or C<sub>1</sub> to C<sub>6</sub> alkoxy, or R<sup>c</sup>R<sup>d</sup><sub>2</sub>Si wherein R<sup>c</sup> is linear or branched C<sub>1</sub> to C<sub>4</sub> alkyl or phenyl, and R<sup>d</sup> is linear or branched C<sub>1</sub> to C<sub>3</sub> alkyl, with a hydride reagent;

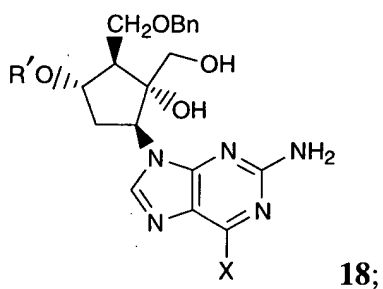
- (b) asymmetrically epoxidizing the product from step (a) with a homochiral diester of tartaric acid, a hydroperoxide, and a metal catalyst to provide the cyclopentane epoxide of the formula



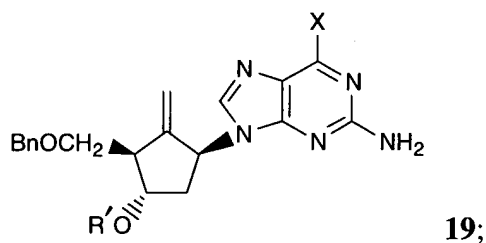
(c) treating the product of step (b) with an alkali metal salt of a purine compound of formula



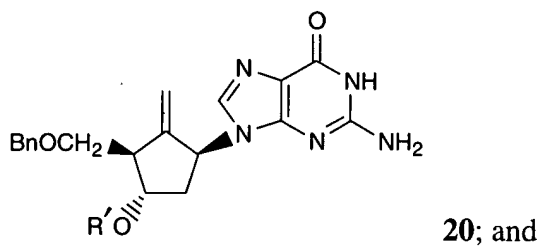
wherein X is Cl, I or BnO, to provide a compound of formula



(d) converting the vicinal diol product of step (c) to an alkene to provide the methylene compound of formula

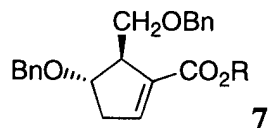


(e) hydrolyzing the X group of the compound of formula **19** to provide the methylene compound of formula



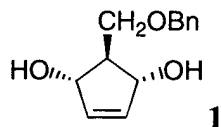
(f) removing the benzyl ether protecting group(s) to provide the compound of formula **21**.

66. A process for the preparation of an ester of the formula

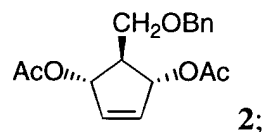


wherein R is C<sub>1</sub> to C<sub>4</sub> alkyl or benzyl, comprising:

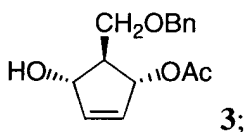
(a) acetylating a diol of the formula



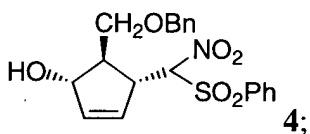
with an anhydride to provide the diacetate of the formula



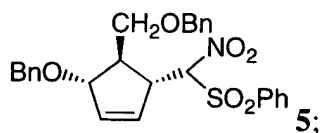
(b) hydrolyzing the product from step (c) with a hydrolase enzyme to give a compound of formula



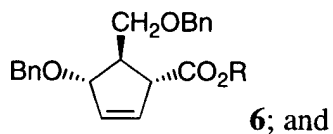
(c) coupling the product from step (b) with phenylsulfonylnitromethane to give a compound of formula



(d) alkylating the product from step (c) with a benzyl halide to provide the compound of formula

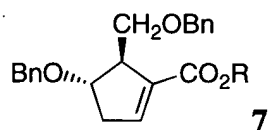


(e) converting the product from step (d) to an ester of the formula



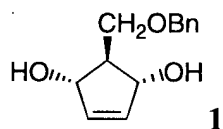
(f) isomerizing the ester of the formula 6 under basic conditions to provide the ester of the formula 7.

67. A process for the preparation of an ester of the formula

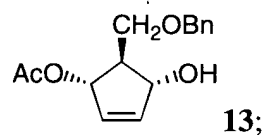


wherein R is C<sub>1</sub> to C<sub>4</sub> alkyl or benzyl, comprising:

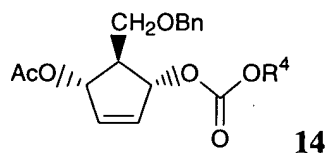
(a) asymmetrically acetylating the diol of the formula



with a C<sub>1</sub> to C<sub>6</sub> alkyl acetate ester and hydrolase enzyme to obtain a compound of formula

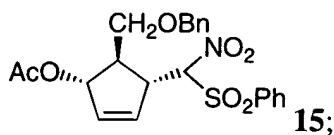


(b) acylating the product from step (a) to give an alkyl carbonate of the formula

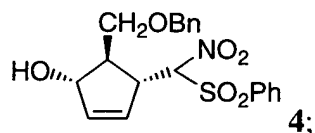


wherein R<sup>4</sup> is C<sub>1</sub> to C<sub>6</sub> alkyl, benzyl, phenyl, or phenyl substituted by C<sub>1</sub> to C<sub>6</sub> alkyl or C<sub>1</sub> to C<sub>6</sub> alkoxy;

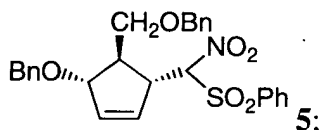
(c) coupling the product from step (b) with phenylsulfonylnitromethane to obtain a compound of formula



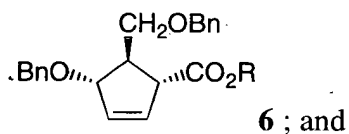
(d) hydrolyzing the product from step (c) with a base to obtain a compound of formula



(e) alkylating the product from step (d) with a benzyl halide in the presence of strong non-nucleophilic base to give the compound of formula

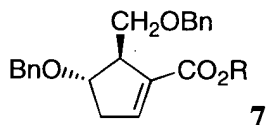


(f) converting the product from step (e) to an ester of the formula



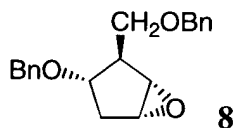
(g) isomerizing the ester of the formula **6** under basic conditions to provide the ester of the formula **7**.

68. A process for the preparation of an ester of the formula

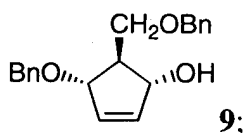


wherein R is C<sub>1</sub> to C<sub>4</sub> alkyl or benzyl, comprising:

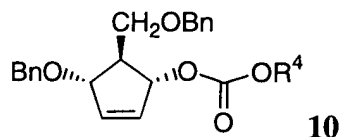
(a) reacting a cyclopentane epoxide of the formula



with a strong non-nucleophilic base to form an allylic alcohol of the formula

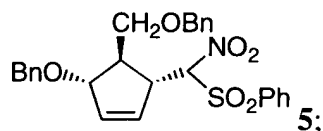


(b) acylating the product from step (a) to give an alkyl carbonate ester of the formula

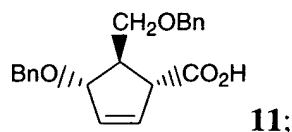


wherein  $R^4$  is  $C_1$  to  $C_6$  alkyl, benzyl, phenyl, or phenyl substituted by  $C_1$  to  $C_6$  alkyl or  $C_1$  to  $C_6$  alkoxy;

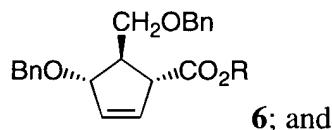
(c) coupling the product of step (b) with phenylsulfonylnitromethane to give the compound of formula



(d) converting the product from step (c) to an acid of the formula

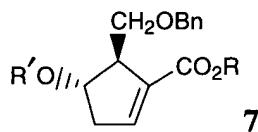


(e) converting the product from step (d) to an ester of the formula



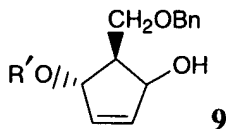
(f) isomerizing the product from step (e) under basic conditions to provide the ester of formula **7**.

69. A process of preparing an ester of the formula

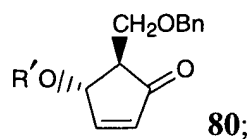


wherein  $R$  is  $C_1$  to  $C_4$  alkyl, or benzyl;  $R'$  is benzyl, or benzyl substituted on the phenyl moiety by  $C_1$  to  $C_6$  alkyl or  $C_1$  to  $C_6$  alkoxy, or  $R^cR^d_2Si$ , wherein  $R^c$  is  $C_1$  to  $C_4$  alkyl, or phenyl, and  $R^d$  is  $C_1$  to  $C_3$  alkyl; comprising:

(a) oxidizing an allylic alcohol of the formula

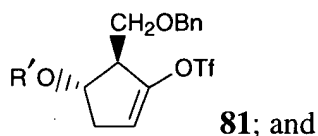


with an oxidizing agent to give a cyclopentenone of the formula



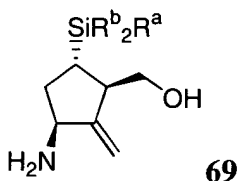
(b) reducing the cyclopentenone of the formula **80** with lithium tri-*sec*-butylborohydride;

(c) sulfonylating the product of step (b) with a triflating reagent to give a compound of formula



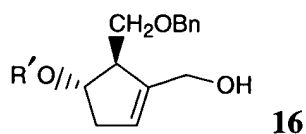
(d) converting the triflate moiety of the compound of formula **81** to an alkoxycarbonyl moiety to give the ester of the formula **7**.

70. A compound of formula



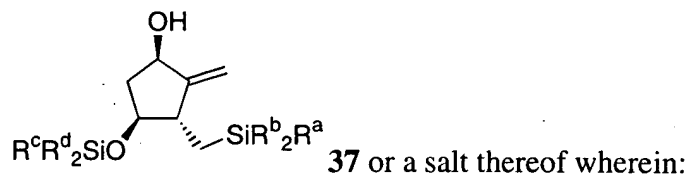
wherein  $R^a$  is allyl, phenyl,  $C_1$  to  $C_6$  alkylphenyl or  $C_1$  to  $C_6$  alkoxyphenyl; and  $R^b$  is  $C_1$  to  $C_6$  alkyl; or a salt thereof.

71. A compound of formula



or a salt thereof wherein  $R^1$  is benzyl or  $R^cR^dSi-$ ,  $R^c$  is  $C_1$  to  $C_4$  alkyl or phenyl, and  $R^d$  is  $C_1$  to  $C_3$  alkyl.

72. A compound of formula



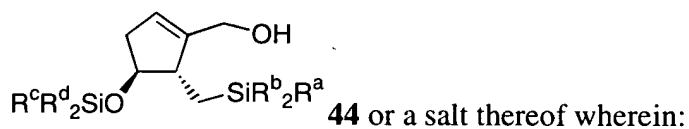
$R^a$  is allyl, phenyl,  $C_1$  to  $C_6$  alkylphenyl or  $C_1$  to  $C_6$  alkoxyphenyl;

$R^b$  is  $C_1$  to  $C_6$  alkyl;

$R^c$  is  $C_1$  to  $C_4$  alkyl or phenyl; and

$R^d$  is  $C_1$  to  $C_3$  alkyl.

73. A compound of formula



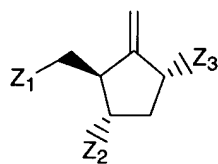
$R^a$  is allyl, phenyl,  $C_1$  to  $C_6$  alkylphenyl or  $C_1$  to  $C_6$  alkoxyphenyl;

$R^b$  is  $C_1$  to  $C_6$  alkyl;

$R^c$  is  $C_1$  to  $C_4$  alkyl or phenyl; and

$R^d$  is  $C_1$  to  $C_3$  alkyl.

74. A compound of formula



wherein  $Z_1$  and  $Z_2$  are both  $R^cR^d_2SiO-$  and  $Z_3$  is hydroxy or  $Z_1$  and  $Z_2$  are both hydroxy and  $Z_3$  is  $R^cR^d_2SiO-$ ;

$R^c$  is  $C_1$  to  $C_4$  alkyl or phenyl; and

$R^d$  is  $C_1$  to  $C_3$  alkyl.